SYNTHESIS AND STUDY OF BIOLOGICAL ACTIVITY OF SOME NOVEL THIAZOLIDINONES AND AZETIDINONES COMPOUNDS

A Schiff base, named after Hugo Schiff, is a compound having a functional group which contains a carbon-nitrogen double bond and the nitrogen atom connected to an aryl or alkyl group, not to hydrogen.**[1]** Schiff bases in a broad sense have the general formula $R^1R^2C=NR^3$, where R is an organic side chain. Schiff base is synonymous with azomethine. Some restrict the term to the secondary aldimines (azomethines where the carbon is connected to a hydrogen atom), having the general formula RCH=NR'.**[2]**

The chain on the nitrogen makes the Schiff base a stable imine. A Schiff base derived from an aniline, where R^3 is a phenyl or a substituted phenyl, can be called an anil.**[3].** Numbers of biological activities such as antimicrobial, antimalarial, anticancer, antimycobacterial and anti-inflammatory have been observed for various schiff bases. **[4-12]**.

4-Thiazolidinones play a vital role owing to their wide range of pharmacological activities. They have been found to be associated with diverse biological activities and reports have appeared in literatures which highlight their chemistry and uses. They possess various potent anti-HIV, antimicrobial, analgesic, anti-inflammatory and antitumor activities. **[13-35]**.

The 2-azetidinone nucleus has been recognized as the central moiety of the β-lactam antibiotics, the most widely employed family of antimicrobial agents to date. Furthermore, the recent discoveries of some azetidinones display a broad range of biological activity *viz*. antimicrobial, anti-inflammatory, analgesic, CNS depressant and antitubercular. Beside their significance as bioactive agents, they are also important as synthetic intermediates **[36-55]**.

Venlafaxine hydrochloride is a well known pharmaceutically active compound and used as a CNS agent in the treatment of Antidepressant **[56]**. 1-(2-amino-1-(4-methoxyphenyl) ethyl) cyclohexanol is a leading active metabolite, which is one of the key intermediate to venlafaxine hydrochloride. We have planned to apply 1-(2-amino-1-(4-methoxyphenyl) ethyl) cyclohexanol as a starting building block and synthesized newer analogs of Schiff bases, thiozolidinones and Azetidinone for their microbial activities study.

The Thesis will consist of **four** chapters;

Chapter I : Introduction & literature review of Schiff base, scope of the present work & synthesis of 2-(2-substitutedbenzylidenehydrazinyl)-N-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl) acetamides.

Chapter II : Introduction & literature review, experimental reaction, physical properties, spectral studies & microbial studies of 4-thiazolidinone ;

2-(4-oxo-2-substitutedphenylthiazolidin-3-ylamino)-N-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl) acetamide

Chapter III : Introduction & literature review, experimental reaction, physical properties, spectral studies& microbial studies of 2-azetidinones;

2-(3-chloro-2-oxo-4-substitutedphenylazetidin-1-ylamino)-N-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)acetamides

Chapter IV : Overall results & conclusions

Analysis

All the newly synthesized compounds have been studied by elemental and spectral analysis. Minimum inhibitory concentration (MIC) of all the synthesized compounds was determined against four different strains, *viz.* two Gram positive bacteria (*S. aureus & S. pyogenes)* and two Gram negative bacteria (*E. coli & P. aeruginosa*) and compared with standard drugs gentamycin, ampicillin, chloramphenicol, ciprofloxacin, & norfloxacin by broth dilution method. Antifungal activities against *C. albicans*, *A. niger* and *A. clavatus* were compared with standard drugs nystatin and greseofulvin by same method and some compounds were screened against ***Mycobacterium tuberculosis*** and compared with standard drug Rifampicin **[57]**.Also some compounds were screened for ***anti-HIV activity*** and compared with standard drugs Nevirapine, Azidothymidine, Didieoxydinine and Dideioxyinosine **[58].**

The synthesized compounds are expected to exhibit moderate to very good biological activity.

Reference:

1. IUPAC, Compendium of Chemical Terminology, 2nd ed. (the "Gold Book") (1997). Online corrected version: (2006–) "Schiff base".

2. IUPAC, Compendium of Chemical Terminology, 2nd ed. (the "Gold Book") 1997). Online corrected version: (2006–) "azomethines".

3. IUPAC, Compendium of Chemical Terminology, 2nd ed. (the "Gold Book") (1997). Online corrected version: (2006–) "anils".

4. Srivastava, S. K.; Sonwane, S. K.; Verma, Smita, International Journal of Pharmaceutical Sciences (Bangalore, India) (2010), 2(3), 656-663. Publisher: Pharmaceutical Scientific Society, CODEN: IJPSOO. ISSN: 0975-4725.

5. Joshi, Aakanksha; Narayanaswamy, Venugopala Katharigatta; Rao, Gopal Krishna; Devi, Kalpana; Pathak, Arun. Indian Journal of Heterocyclic Chemistry (2011), 20(3), 295-296. Publisher: Prof. R. S. Varma, CODEN: IJCHEI ISSN: 0971-1627.

6. Patil, Sharanabasappa B.; Goudgaon, Naganna M. International Journal of Pharmaceutical Sciences and Research (2010), 1(6), 50-56.

7. Sharma, M. C.; Kohli, D. V.; Sharma, Smita; Sharma, A. D. Chemica Sinica (2010),1(1), 73-85. Publisher: Pelagia Research Library, CODEN: CSHIA5 ISSN: 0976-8505.

8. Patel, Navin B.; Shaikh, Faiyazalam M, Saudi Pharmaceutical Journal (2010), 18(3), 129-136.

9. Shreenivas, M. T.; Chetan, B. P.; Bhat, A. R., Journal of Pharmaceutical Science & Technology (2009), 1(2), 88-94.

10. Chen, Hua; Guo, Zaihong; Yin, Qingmei; Duan, Xiaoxu; Gu, Yunjing; Li, Xiaoliu. Frontiers of Chemical Science and Engineering (2011), 5(2), 231-237.

11. Singh, Tej Prakash; Sharma, Pramod Kumar; Kaur, Preet Kanwal; Mondal, Sombhu Charan; Gupta, Amit, Pharma Chemica (2011), 3(1), 194-206.

12. Pitta, Eleni; Crespan, Emmanuele; Geronikaki, Athina; Maga, Giovanni; Samuele, Alberta. Letters in Drug Design & Discovery (2010), 7(4), 228-234.

13. Chawla, Pooja; Singh, Ranjit; Saraf, Shailendra K., . Medicinal Chemistry Research No pp. yet given. Publisher: Birkhaeuser Boston, CODEN: MCREEB ISSN: 1054-2523.

14. Patel N.B. and Patel V.N., Indian J. Hetero. Chem.; 16, 2007, 247.

15. Rawal R.K., Tripathi R., Katti S.B., Pannecouquec C. and Clercq E.D.; Bioorg. Med. Chem. 15, 2007, 1725.

16. Rawal R.K., Tripathi R., Katti S.B., Pannecouque C. and Clercq E.D.; Eur. J. Med. Chem., 43, 2008, 2800.

17. Rana P.B., Mistry B.D. and Desai K.R.; Arkivoc, xv, 2008, 262.

18. Ramalakshmi N., Aruloly L., Arunkumar S., Ilango K. and Puratchikody A.; Malaysian J. Sci., 28, 2009, 197.

19. Ronad P.M., Noolvi M.N., Sapkal S., Dharbhamulla S., and Maddi V.S.; Eur. J. Med. Chem.45, 2010, 85.

20. Kuecuekguezel, Gueniz; Kocatepe, Ayla; De Clercq, Erik; Sahin, Fikrettin; Guelluece, Medine. European Journal of Medicinal Chemistry (2006), 41(3), 353-359.

21. Sriram, D.; Yogeeswari, P.; Kumar, T. G. Ashok. Indian Journal of Pharmaceutical Sciences (2005), 67(4), 496-499.

22. Rawal, Ravindra K.; Prabhakar, Yenamandra S.; Katti, S. B.; De Clercq, E. Bioorganic & Medicinal Chemistry (2005), 13(24), 6771-6776.

23. Rawal, Ravindra K.; Solomon, V. Raja; Prabhakar, Yenamandra S.; Katti, S. B.; De Clercq, E. Combinatorial Chemistry and High Throughput Screening (2005), 8(5), 439-443.

24. Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappala, M. Antiviral Research (2004), 63(2), 79-84. Publisher: Elsevier B.V., CODEN: ARSRDR ISSN: 0166-3542.

25. Chen, Hua; Guo, Zaihong; Yin, Qingmei; Duan, Xiaoxu; Gu, Yunjing; Li, Xiaoliu. Frontiers of Chemical Science and Engineering (2011), 5(2), 231-237.

26. Singh, Tej Prakash; Sharma, Pramod Kumar; Kaur, Preet Kanwal; Mondal, Sombhu Charan; Gupta, Amit. Pharma Chemica (2011), 3(1), 194-206.

27. Rawal, Ravindra K.; Tripathi, Rajkamal; Katti, S. B.; Pannecouque, Christophe; De Clercq, Erik. European Journal of Medicinal Chemistry (2008), 43(12), 2800-2806.

28. Rawal, Ravindra K.; Tripathi, Rajkamal; Kulkarni, Smitha; Paranjape, R.; Katti, S. B.; Pannecouque, Christophe; De Clercq, Erik. Chemical Biology & Drug Design (2008), 72(2), 147-154.

29. Rawal, Ravindra K.; Tripathi, Raj Kamal; Katti, S. B.; Pannecouque, Christophe; De Clercq, Erik. Medicinal Chemistry (2007), 3(4), 355-363.

30. Balzarini, Jan; Orzeszko, Barbara; Maurin, Jan K.; Orzeszko, Andrzej. European Journal of Medicinal Chemistry (2007), 42(7), 993-1003.

31. Samadhiya, Pushkal; Sharma, Ritu; Srivastava, Santosh K.; Srivastava, Savitri D. Chinese Journal of Chemistry (2011), 29(5), 1001-1010.

32. Jubie, S.; Gowramma, B.; Nitin, K. M.; Jawahar, N.; Kalirajan, R.; Gomathy, S.; Sankar, S.; Elango, K. International Journal of Pharmaceutical Sciences (Chennai, India) (2009), 1(1), 32-38.

33. Raga, Basawaraj; Amith, L.; VijayKumar, T.; Havangirao, M.; Upendra, C. H. International Journal of ChemTech Research (2010), 2(3), 1764-1770.

34. Aridoss, G.; Amirthaganesan, S.; Kim, M. S.; Kim, J. T.; Jeong, Yeon Tae. European Journal of Medicinal Chemistry (2009), 44(10), 4199-4210.

35. Kamel M.M., Ali H.I., Anwar M.M., Mohamed N.A., and Soliman A.M.; Eur. J. Med. Chem., 45, 2010, 572.

36. Patel R.B., Desai P.S., Desai K.R. and Chikhalia K.H.; Indian J. Chem., 45B, 2006,773.

37. Bhati S. and Kumar A.; Eur. J. Med. Chem.; 43, 2008, 2323.

38. Gurupadayya B.M., Gopal M., Padmashali B. and Manohara Y.N.; Indian J. Pharm. Sci., 70, 2008, 572.

39. Patel N. B. and Patel J. C.; J. Saudi chem. Soc., 12, 2008, 121.

40. Ansari K.F and Lal C.; J. Chem. Sci., 121, 2009, 1017.

41. Kumar A. and Rajput C.; Eur. J. Med. Chem., 44, 2009, 83.

42. Ameya A. Chavan and Nandini R. Pai, ARKIVOC 2007 (xvi) 148-155.

43. Ameya A. Chavan and Nandini R. Pai , *Molecules* 2007*, 12,* 2467-2477.

44. Rajasekaran, A.; Periasamy, M.; Venkatesan, S. Journal of Developmental Biology and Tissue Engineering (2010), 2(1), 5-13.

45. Raga, Basawaraj; Amith, L.; VijayKumar, T.; Havangirao, M.; Upendra, C. H. International Journal of ChemTech Research (2010), 2(3), 1764-1770.

46. Rokade, Y.; Dongre, N.; Engla, G.; Behera, C.; Sayyed, R. Asian Journal of Microbiology, Biotechnology & Environmental Sciences (2010), 12(1), 109-114.

47. Magtoof, Mahmood Shakir; Hassan, Z. S.; Hello, Kasim Mohammed. Organic Chemistry: An Indian Journal (2011), 7(4), 219-227.

48. Baviskar, B. A.; Shiradkar, M. R.; Khadabadi, S. S.; Deore, S. L.; Bothara, K. G. Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (2011), 50B (3), 321-325.

49. Kumar, Sushil; Chandna, Manish; Gupta, Mohit. Journal of Pharmacy Research (2010), 3(12), 3010-3012.

50. Mathew, Githa Elizebeth; Mathew, Nirmal; Vijayabaskaran, M. Pharma Chemica (2010), 2(6), 238-242.

51. Chopde, Himani N.; Pagadala, Ramakanth; Meshram, Jyotsna S.; Jetti, Venkateshwarlu. Journal of Heterocyclic Chemistry (2010), 47(6), 1361-1366.

52. Murhekar, M. M.; Khadsan, R. E. Pharma Chemica (2010), 2(4), 219-223.

53. Rajasekaran, A.; Periasamy, M.; Venkatesan, S. Journal of Developmental Biology and Tissue Engineering (2010), 2(1), 5-13.

54. Singh, Indu; Kaur, Hemlata; Kumar, Sunil; Lata, Suman; Kumar, Arun; Kumar, Ashok. International Journal of Pharma Sciences and Research (2010), 1(2), 148-168.

55. Chhajed, Santosh S.; Manisha, Puranik; Bastikar, Virupaksha A.; Animeshchandra, Haldar; Ingle, V. N.; Upasani, Chandrashekhar D.; Wazalwar, Sachin S. Bioorganic & Medicinal Chemistry Letters (2010), 20(12), 3640-3644.

56. G.E.M. Husbands et al., EP 112669; US 453186 (1984, 1985 both to Am. Home prods.).

57. (a) Rattan A., Antimicrobials in laboratory medicine, Churchill B. I., Livingstone, New Delhi; 2000, 85-108.
(b) European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

58. Abbott W S, J Econ Ent 18, 1925,801.

Dr. Sunil I. Marjadi
Principal
KBS Group of Institutions
NATARAJ Professional Sciences College
Chanod Colony, Naka, Vapi.

(Dr. SUNIL I. MARJADI)
Signature of the Supervising Teacher

(VINAY MAHYAVANSHI)
Signature of the Student